I. AMENDMENT

Please amend specification from page 2, line 34 to page 4, line 6 as follows. Because some of the text was originally in underlined, the specific changes requested are summarized in the remarks section below:

Despite its name, Peptide Nucleic Acid (PNA) is neither a peptide, a nucleic acid nor is it an acid. Peptide Nucleic Acid (PNA) is a non-naturally occurring polyamide that can hybridize to nucleic acid (DNA and RNA) with sequence specificity (See: United States Patent No. 5,539,082 and Egholm et al., *Nature 365*: 566-568 (1993)). Being a non-naturally occurring molecule, unmodified PNA is not known to be a substrate for the enzymes that are known to degrade peptides or nucleic acids. Therefore, PNA should be stable in biological samples, as well as have a long shelf-life. Unlike nucleic acid hybridization which is very dependent on ionic strength, the hybridization of a PNA with a nucleic acid is fairly independent of ionic strength and is favored at low ionic strength, conditions that strongly disfavor the hybridization of nucleic acid to nucleic acid (Egholm et al., *Nature*, at p. 567). The effect of ionic strength on the stability and conformation of PNA complexes has been extensively investigated (Tomac et al., *J. Am. Chem. Soc.* ~~*118*:55 44-5552~~ *118*: 5544-5552 (1996)). Sequence discrimination is more efficient for PNA recognizing DNA than for DNA recognizing DNA (Egholm et al., *Nature*, at p. 566). However, the advantages in point mutation discrimination with PNA probes, as compared with DNA probes, in a hybridization assay, appears to be somewhat sequence dependent (Nielsen et al., *Anti-Cancer Drug Design* ~~*8*:53-65~~ *8*:53-63, (1993) and Weiler et al., *Nucl. Acids Res. 25:* 2792-2799 (1997)).

Though they hybridize to nucleic acid with sequence specificity (See: Egholm *et al., Nature*, at p. 567), PNAs have been slow to achieve commercial success at least partially due to cost, sequence specific properties/problems associated with solubility and self-aggregation (See: Bergman, F., Bannwarth, W. and Tam, S., *Tett. Lett. 36*:6823-6826 (1995), Haaima, G., Lohse, A., Buchardt, O. and Nielsen, P.E., *Angew. Chem. Int. Ed. Engl. 35*:1939-1942 (1996) and Lesnik, E., Hassman, F., Barbeau, J., Teng, K. and Weiler, K., *Nucleosides & Nucleotides 16*:1775-1779 (1997) at p 433, col. 1, ln. 28 through col. 2, ln. 3) as well as the uncertainty pertaining to non-specific interactions that might occur in

complex systems such as a cell (See: Good, L. et al., *Antisense & Nucleic Acid Drug Development* 7:431-437 (1997)). However, problems associated with solubility and self-aggregation have recently been reduced or eliminated (See: Gildea et al., *Tett. Lett. 39:* 7255-7258 (1998)). Nevertheless, their unique properties clearly demonstrate that PNA is not the equivalent of a nucleic acid in either structure or function. Consequently, PNA probes need to be evaluated for performance and optimization to thereby confirm whether they can be used to specifically and reliably detect a particular nucleic acid target sequence, particularly when the target sequence exists in a complex sample such as a cell, tissue or organism.

DNA and PNA probes targeting rRNA have been used for the detection of bacteria (gonorrhoeae and mycobacteria) and eucarya by *in situ* hybridization (See: WO95/32305 (now US 5,985,563), WO98/15648; and WO97/18325 (now US ~~5,888,737~~ 5,888,733) respectively). PNA probes have also been used to examine telomeres and repeat sequences by *in-situ* hybridization (See: WO97/14026). Methods for the linking of enzymes to both DNA and PNA probes are known in the art (See: WO99/41273). However, the use of enzyme-labeled DNA probes for the detection of yeast cells by *in-situ* hybridization has not yet been demonstrated (Amann, R. I., Zarda, B., Stahl, D.A. and Schleifer, K.-H., **Identification of individual prokaryotic cells by using enzyme-labeled, rRNA-targeted oligonucleotide probes,** *Applied and Environmental Microbiology, 58:* 3007-3011 (1992)) and Applicants are unaware of any attempts to use enzyme-labeled PNA probes to detect yeast by *in-situ* hybridization. The lack of examples of successful ISH assays utilizing enzyme linked probes likely results because of difficulties in getting such large molecules to pass through the cell membrane into the yeast cytoplasm.